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HFRS and hantaviruses in the Balkans/South-East Europe

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ABSTRACT

Hemorrhagic fever with renal syndrome is endemic in the Balkans with epidemic outbreaks and sporadic cases that have been recorded yearly since the disease was first recognized. The incidence of Balkan HFRS is modest, with approximately one hundred cases reported in most years. Seroepidemiological investigations conducted in several Balkan countries revealed an overall seroprevalence of 6% in Bosnia and Herzegovina, 1.6% in Croatia, 4% in Greece and 1.7% in Slovenia, respectively. The complex ecology of the Balkan Peninsula supports the existence of diverse rodent and insectivore species which harbor several pathogenic and non-pathogenic hantaviruses. Among them only Dobrava (DOBV) and Puumala (PUUV) viruses are associated with disease in humans. Comprehensive clinical studies compared clinical signs and symptoms between patients infected with either virus. A spectrum of clinical picture of the disease ranges from mild illness typical of PUUV infections to a severe form with fulminant hemorrhagic fever and an overall mortality rate of 9.8% among DOBV infected patients. While severe DOBV cases are recognized from Slovenia in the North to Greece in the South, PUUV infections are more frequent in northern part of the area. Balkans represent an area with a potential need for hantavirus vaccines, but due to co-existence of DOBV and PUUV causing HFRS in the same region, a universal vaccine is required.

1. Historical perspectives

Hemorrhagic fever with renal syndrome is endemic in the Balkan Peninsula, and may have existed there for decades. The first probable case of HFRS was reported in the former Yugoslavia in 1952 as a case of acute renal failure successfully treated by peritoneal dialysis (Simic, 1952). The patient was a soldier who was infected in the forest surrounding Fojnica in Bosnia and Herzegovina (B&H), where, in the later outbreaks, hundreds of HFRS cases

infected during the season timberwork in the forest of Pohorje in Slovenia. At the time, the authors were already aware of the clinical resemblance of the disease to that occurring in Scandinavia; therefore they named it Nephropathia Epidemica (Radosevic and Mohacek, 1954). Afterwards, clinical cases of HFRS were also reported from Albania (Eltari et al., 1987), Bulgaria (Verbev and Gabev, 1963), Greece (Antoniadis et al., 1984) and Romania (Manasia et al., 1977).

Epidemic outbreaks as well as sporadic cases have been recorded yearly, since the disease was first recognized in South-East Europe. The first documented epidemic of HFRS occurred in a military camp in the forest of Fruška Gora in Serbia in 1961 (Heneberg et al., 1964). A second epidemic in 1967, affecting more than 200 individuals with 5 fatalities, was centered in Bosnia and Herzegovina (Fojnica and Foča) and in Croatia (Plitvice Lakes) (Vesenjak-Hirjan et al., 1971). In summer of 1983 an outbreak of HFRS occurred in the state of Epirus, north-western Greece. A

persons with symptoms clinically compatible with a diagnosis of HFRS were officially reported in 1986 from all republics and provinces of the former Yugoslavia with the highest incidence in Montenegro (Avšič-Županc et al., 1989; Gligic et al., 1989). A nation-wide epidemic of HFRS occurred in all six republics and two provinces of former Yugoslavia in 1989 when 226 HFRS cases were serologically confirmed. The severity of disease differed from region to region, with an overall fatality of 6.6% (Gligic et al., 1992). One of the largest outbreaks of HFRS took place in the Balkan region during the war in 1995 when clinical diagnosis was serologically confirmed in 128 patients, mainly soldiers, from the Tuzla region in B&H (Hukic et al., 1996) and in 85 patients, mostly soldiers (3 fatal), from several localities in Croatia (Kuzman et al., 1997; Markotić et al., 1996, 2002b). The next epidemic year that have affected Balkan countries was in 2002 with >500 clinically diagnosed patients mainly registered in Croatia, Slovenia and B&H (Heyman et al., 2009; Hukic et al., 2010; Koren et al., 2008;

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Kuzman et al., 2003). The same year an unusual outbreak of 11 HFRS cases appeared among former injecting drug users in the drug-treatable community Susret, Ivanovac, northeast of Croatia (Medved et al., 2002). In the following years of 2005 and 2008 an increased hantavirus activity was noticed again in Slovenia, Croatia and B&H (Heyman et al., 2011; Kraigher et al., 2012). The largest epidemic of HFRS so far occurred in 2012 in Slovenia and Croatia, with 188 and 184 laboratory confirmed cases, respectively.

2. Ecology

The ecology of hantaviruses in the Balkan Peninsula is complex, given the existence of diverse rodent species, which reflects the geographic location of the Balkan States at the meeting points of Europe, Asia, and North Africa. By the detection of viral antigen, antibody, RNA amplification or virus isolation the presence of several pathogenic and non-pathogenic hantaviruses has been demonstrated in the region. They are associated with four rodent genera: *Apodemus*, *Myodes*, *Microtus*, and *Rattus*; and also with insectivore carriers. The most prominent hantavirus carrier in the Balkans is the yellow necked mouse, *A. flavicollis*, host of Dobrava virus (DOBV), which is generally widespread throughout the region. These rodents prefer mature deciduous forests with areas where sufficient plant diversity ensures an adequate food supply each year (Kryštufek, 1991; Vukićevič-Radić et al., 2006). Following a number of severe HFRS cases in the southeastern part of Slovenia, DOBV was isolated in 1988, from the lungs of the yellow necked mouse captured in Dobrava village. In 1992, it was fully characterized and recognized as a unique hantavirus species (Avšič-Županc et al., 1992). Subsequently, the presence of DOBV in hosts and humans was reported from several countries in South-East Europe: Albania, B&H, Bulgaria, Croatia, Greece, Romania, Serbia and Montenegro (reviewed in Heyman et al., 2009). Another *Apodemus* host, *A. agrarius* or striped field mouse, is commonly found in grassy fields, cultivated areas and woodlands of the Balkans (Kryštufek, 1991; Vukićevič-Radić et al., 2006) and it is a reservoir host for Saaremaa virus (SAAV) (Plyusnin et al., 1997, 1999). Recently it was suggested to classify SAAV from outside Saaremaa island as Kurkino genetic lineage of DOBV. DOBV-Kurkino is responsible for a milder form of HFRS in Central Europe (Klempa et al., 2013), but in the Balkan region the virus was demonstrated only in rodents from Slovenia and Croatia (Avšič-Županc et al., 2000; Plyusnina et al., 2011). In south Balkan countries, like Greece, Romania, Albania, Macedonia, Serbia and Montenegro, almost all HFRS cases are cause by DOBV, but to the north, more Puumala virus (PUUV) infections are observed. For example in Slovenia and Croatia approximately 70% of HFRS cases are caused by PUUV. The major carrier of PUUV is *Myodes glareolus* or bank vole, which inhabits mostly wet coniferous and mixed forests to leafed forests, river banks and marshy areas in the Balkans (Kryštufek, 1991). In concordance with numerous HFRS cases caused by PUUV in Slovenia, Croatia and B&H high antibody prevalence in bank voles was reported (Avšič-Županc et al., 2007; Hukic et al., 2003; Tadin et al., 2012). The prevalence of hantavirus antibodies and antigens was detected on average in 16% of *A. flavicollis*, 8.1% *A. agrarius* and 16% of *M. glareolus*, but a significant difference was observed between epidemic and non-epidemic years. While during the non-epidemic years the prevalence of hantaviruses in hosts in endemic areas of HFRS in the former Yugoslavia was on average 9.2%, the prevalence of infection was on average 19.7% and 23% for the epidemic years 1986 and 1989, respectively (Avšič-Županc et al., 1990, 1993; Avšič-Županc and Poljak, 1994; Gligic et al., 1992; Lukač et al., 1990). Despite some evidence of possible human infection with TULV in Central Europe (Vapalahti et al., 1996), currently no clinical case due to TULV infection has been reported in the Balkan Peninsula. However, TULV RNA was amplified from tissue samples of *M. arvalis*, *M. agrestis* and *M. subterraneus* (re-classified from *Pitymys subterraneus*) in Slovenia, Croatia and Serbia (Korva et al., 2009; Scharninghausen et al., 2002; Song et al., 2002). Moreover, as early as in 1989 there were reports of hantaviral antigens discovered in tissues of Eurasian common shrews (*Sorex araneus*), alpine shrews (*Sorex alpinus*), Eurasian water shrews (*Neomys fodiens*) and common moles (*Talpa europea*) in areas of the former Yugoslavia (Gligic et al., 1992). Later, in 2013 Seewis virus RNA was amplified from tissues of *S. araneus* captured in Slovenia (Resman et al., 2013).

3. Epidemiology

HFRS cases in the Balkan Peninsula are reported yearly, either as sporadic cases or major outbreaks influenced by the abundance of reservoir rodent populations (Table 1). The incidence of the disease is modest, with approximately 100 cases per year (Heyman et al., 2009), but, due to DOBV infection, the mortality can be high (on average 12%) (Avšič-Županc et al., 1999). Also, apparent seasonal distribution, with most cases occurring in the summer months is observed. Occupation is a dominant risk factor, with animal trappers, forestry workers, farmers and military personnel at highest risk (Heyman et al., 2009).

3.1. Albania and Macedonia

In Albania, the first serologically confirmed HFRS case dates to 1987, when a 27-year old man presented with acute renal failure and shock (Eltari et al., 1987). Also, in a HFRS epidemic, which occurred in Yugoslavia in 1986, 4 out of 6 Albanian patients had antibodies against hantaviruses (Gligic et al., 1989). In a study performed between 2003 and 2006, 11.7% of the patients with clinical suspicion of CCHF were actually confirmed as HFRS cases, which suggest that there are more unrecognized, severe HFRS cases in Albania (Papa et al., 2008).

The first report of a HFRS case in the Republic of Macedonia dates to 1987. In a 3-year period, from 1987 to 1990, at least 10 DOBV cases were diagnosed, with a 10% mortality rate (Polenakovic et al., 1995).

3.2. Bosnia and Herzegovina

B&H has been recognized as a highly endemic region in the Balkans for over 50 years. In addition to PUUV and DOBV, also a Seoul virus was also identified as a potential cause of HFRS in B&H (Clement et al., 1994; Lundkvist et al., 1997; Markotić et al., 1995). Infections caused by PUUV are more frequent (49.6%) than infections caused by DOBV (26.1%) during both epidemic and non-epidemic periods (Hukic et al., 2011). Since the first documented HFRS outbreak in 1967 more than 732 cases have been reported (Heyman et al., 2011). Most HFRS cases have been observed as large outbreaks, with significant number of patients and mortality varying from 4.86% in 1989 up to 7.3% in 1995 (Gligic et al., 1992; Markotić et al., 1996). The seroprevalence in the general population in B&H is 7.4% in the endemic region and 2.4% in the non-endemic region (Hukic et al., 2010). Former soldiers, as an occupational risk group, have significantly higher seroprevalence (16.1%) compared to the general population (6.2%) in the same area. In a comparison of the seroprevalence of PUUV and DOBV among healthy individual in endemic regions it was noted that antibodies against PUUV are present in almost 6% of population, while DOBV seroprevalence is only 1.5%. The difference is probably due to the fact that DOBV causes a more severe form of HFRS and consequently less cases remains undetected (Hukic et al., 2010).

Table 1
HFRS cases in the Balkan countries registered during the period from 1952 to 2012.

Year/country	Albania[a] and Macedonia[b]	Bosnia and Herzegovina[c]	Bulgaria[d]	Croatia[e]	Greece[f]	Serbia[g] and Montenegro[h]	Slovenia[i]	Romania[j]
1952–1960	–	1	97	3	–	1	1	27
1961	–	–	8	–	–	46	–	
1962–1966	–	–	53	–	–	–	–	
1967	–	160	33	14	–	–	–	
1968–1982	–	–	172	4	–	3	–	–
1983	0	3	7	1	8	1	1	–
1984–1985	0	7	9	7	13	9	6	–
1986	1	15	20	4	–	163	2	–
1987–1988	2	10	–	6	–	13	18	–
1989	6	144	–	27	–	111	12	–
1990–1994	1	19	–	18	–	10	52	–
1995	–	354	–	85	–	–	14	–
1996–2001	–	–	–	39	16	–	36	–
2002	–	136	–	401	8	128	33	–
2003–2004	–	–	–	16	6	65	21	–
2005	–	21	5	24	5	–	24	1
2006–2007	–	34	2	20	9	–	20	3
2008	–	25	4	19	1	–	46	4
2009–2011	–	27	7	21	7	–	36	13
2012	–	36	–	184	–	–	188	–
Total	10	992	417	873	73	550	510	48

"–", no data.
[a] Eltari et al. (1987) and Gligic et al. (1989).
[b] Polenakovic et al. (1995).
[c] Heyman et al. (2011), Heyman and Vaheri (2008), Hukic et al. (1996), Hukic et al. (2003) and Hukic et al. (2011).
[d] Chumakov et al. (1988), Verbev and Gabev (1963), Heyman et al. (2011) and Papa and Christova (2011).
[e] Cvetko et al. (2005), Markotić et al. (1996), Markotić et al. (2002b) and Medved et al. (2002).
[f] Antoniadis et al. (1987), Heyman et al. (2011), Heyman and Vaheri (2008) and Papa and Antoniadis (2001).
[g] Gligic et al. (1992) and Papa et al. (2006).
[h] Gledovic et al. (2008), Gligic et al. (1992) and Papa et al. (2006).
[i] Avšič-Županc et al. (1999), Heyman et al. (2011), Heyman and Vaheri (2008), Koren et al. (2008) and Kraigher et al. (2012).
[j] Heyman et al. (2011), Heyman and Vaheri (2008), Maftei et al. (2012) and Manasia et al. (1977).

3.3. Bulgaria

HFRS has been a notifiable disease in Bulgaria since 1953 and during the period 1954–1986, 399 cases of HFRS were registered, with a 15.8% mortality rate. Serological investigation has confirmed DOBV infection in 90.6% of investigated cases (Chumakov et al., 1988). In the last decade 36 cases have been reported mainly in the southwestern region, in the areas of the Balkan and Rila-Pirin-Rodopa mountain range. Genetic studies have revealed, that Bulgarian DOBV sequences cluster together with sequences from neighboring Greece (Papa and Christova, 2011). Additionally, even in non-endemic regions of the country approximately 2.8% of patients with acute undifferentiated febrile illness are due to hantavirus infections (Christova et al., 2013).

3.4. Croatia

Croatia is an important natural focus for hantaviruses, where the whole country, with the exception of the coastal region and the islands, is endemic for HFRS, either caused by DOBV or PUUV (Markotić et al., 1996). Besides DOBV and PUUV also DOBV-Kurkino genome sequences were found in rodents (*A. agrarius*) in Croatia (Plyusnina et al., 2011), but so far no documented HFRS case has been associated with this virus in the region. Since the first recognition of HFRS patients in 1952 (Radosevic and Mohacek, 1954) HFRS has been regularly occurring in the country, mostly are sporadic cases, with few epidemic outbreaks (Cvetko et al., 2005; Markotić et al., 1996, 2002b; Medved et al., 2002). From 10 to 20 sporadic HFRS cases are reported annually, with two-thirds of the patients infected with PUUV and only one-third with DOBV (Markotić et al., 2002b). A higher proportion of DOBV infections were found in the Dinara mountain, region that was first recognized in the outbreak in 1995 (Kuzman et al., 1997). During the 2002 epidemic, when 401 cases were reported from all over the country, the majority of the disease was recognized in the general population, with only a small number of cases from risk groups (14.9%). Serological analysis revealed DOBV antibodies in only 17 HFRS cases. The clinical manifestations of the disease were observed as 65% mild and only 5% severe, with 1 fatal case (Kuzman et al., 2003). A seroepidemiological investigation among 300 forestry workers and 260 individuals from the general population revealed that antibody prevalence ranged from 0% to 8.9%, with an overall rate of 1.6% (Borčić et al., 1991).

3.5. Greece

The study on HFRS in Greece started in 1980, where the first serological evidence of a HFRS case was presented in 1981 (Lee and Antoniadis, 1981). Although, DOBV is a predominant cause of HFRS cases in Greece, PUUV is also circulating in the country. Most human infections are sporadic, with about five hospitalized cases annually. From the description of the first HFRS cases, and the start of routine diagnostics in 1997 up until 2001, 210 cases were reported (Heyman and Vaheri, 2008; Papa and Antoniadis, 2001). The severity of the disease ranges from a mild or moderate form to severe and fatal cases, but since most cases are caused by DOBV the average mortality rate is high (9%) (Papa and Antoniadis, 2001). The most endemic regions are in the northwest and northeast parts of the country (Pindos and Rodopi mountain range), where 80% of total HFRS cases occurs. No HFRS cases have so far been reported on the islands (Papa and Antoniadis, 2001). Results of serological survey demonstrated an overall seroprevalence of 4%, ranging from 0% up to 14%, where higher percentage was observed among individuals with occupational risks (Antoniadis et al., 1987).

3.6. Serbia and Montenegro

Recognition of HFRS cases in Serbia dates from 1952 and since then most cases have been reported in large epidemics, with an average mortality rate of 10.5% (Gligic et al., 1992). Most DOBV HFRS cases were reported from the south of the country (Leskovac, Vranje, Nis, Surdulica, Vlasina), while PUUV cases are documented in the north (Vojvodina and area near the Drina river). In a recent phylogenetic analysis of DOBV gene sequence amplified from Serbian patients, the sequences clustered together with strains from Slovenia, Slovakia and Greece. Serbian sequences differ by 0.3–2.6% on the nucleotide level in the S segment and by 5.7% on the M segment in comparison with DOBV isolated in Slovenia (Papa et al., 2006).

In Montenegro the first case was recognized in 1967 and since then 4 outbreaks were registered. During the period between 1995 and 2005, 169 cases of HFRS were recognized. The incidence rate was 2.6/100,000 inhabitants, with most cases observed in the rural areas in the northeast of the country (Berane, Plav, Mojkovac, Pluzine and Kolasin). Most HFRS cases (90%) were due to DOBV infection, with an average case fatality rate of 4.8%, ranging from 0.1% to 15% (Gledovic et al., 2008).

3.7. Slovenia

Slovenia is situated in the northern part of the Balkan Peninsula and several hantaviruses coexist in a single region of endemicity. The presence of HFRS in Slovenia was first reported in 1954 (Radosevic and Mohacek, 1954). Soon after the introduction of diagnostic capabilities for hantaviruses, the first evidence of the presence of two hantavirus responsible for human infections in Slovenia was reported (Avšič-Županc et al., 1990). When DOBV was isolated and characterized it became obvious that this virus is responsible for a severe, even fatal form of HFRS (Avšič-Županc et al., 1992, 1994, 1999). In Slovenia, 511 clinically and laboratory confirmed cases of HFRS have occurred sporadically or in small epidemics, so far (Koren et al., 2008; Kraigher et al., 2012); out of them 134 were due to DOBV infection and 377 due to PUUV infection. Besides DOBV-Dobrava genotype also DOBV-Kurkino genotype was discovered in striped field mice in Slovenia (Avšič-Županc et al., 2000), but only recently a first HFRS case, caused by DOBV-Kurkino genotype, has been documented (Korva et al., 2013a, in press). Although HFRS patients have been found throughout the country, most of them have been reported in the endemic regions of Ljubljana and its surroundings, Dolenjska and Štajerska. The clinical severity of the disease caused by PUUV is significantly lower than that of HFRS due to DOBV. The overall mortality rate is 4. 5%, but if only DOBV infections are considered, then the morality rate is 9.8% (Avšič-Županc et al., 1999; Kraigher et al., 2012). In the general Slovenian population, the antibody prevalence against hantaviruses is on average 1.7%, but it varied from 0% to 14.28% when a group of woodworkers was investigated (Avšič-Županc and Poljak, 1994).

3.8. Romania

In Romania the first HFRS cases were clinically diagnosed in 1956 and until 1977, 27 recognized HFRS cases have been documented (Manasia et al., 1977). Up until 2008, when laboratory diagnostic capabilities for hantaviruses was established in the National Reference Laboratory for Vector-Borne Infections, the disease seems to have been completely overlooked in Romania. Retrospectively, 5 HFRS cases were confirmed in a series of patients with unconfirmed leptospirosis hospitalized from 2005 to 2007 (Maftei et al., 2012). Since 2008, an additional 17 HFRS cases were reported and all infections were confirmed as DOBV. Although patients had a severe form of HFRS, in all the outcome of the disease was favorable. Moreover, most HFRS cases were connected with occupational hazards like shepherds or woodcutters (Heyman et al., 2011; Maftei et al., 2012).

4. Clinical aspects

Two hantaviruses, PUUV and DOBV are responsible for clinically manifested HFRS in patients in the Balkans (Avšič-Županc et al., 1999; Markotić et al., 1996, 2002b). There is only anecdotal evidence of possible Seoul virus infection in B&H with a moderate clinical picture and significantly elevated liver transaminases. However, at that time no molecular diagnostic tools were available in the region, so the infection was confirmed only by ELISA and cross reactivity to other hantaviruses was detected as well (Markotić et al., 1995).

4.1. Similarities and differences between Puumala and Dobrava virus infection

Unique situation, where both PUUV and DOBV are circulating in a relatively small region, allowed for comparison of clinical signs and symptoms between patients infected with either virus. Two comprehensive studies were performed describing and comparing characteristics of PUUV or DOBV infection in patients in Slovenia and Croatia (Avšič-Županc et al., 1999; Markotić et al., 2002b). In general, DOBV infections caused a HFRS with moderate to severe clinical picture, while PUUV infections resulted in mild to moderate HFRS, although exceptions were noticed. Using our scale for HFRS disease severity we showed that PUUV infections cause mild clinical manifestations in 65% of patients, 24% patients had a moderate clinical picture, while severe to very severe clinical pictures were recorded in 8% and 3% patients, respectively. In patients with DOBV infections, mild disease was recorded in 44% and moderate in almost the same percentage (40%) of patients, while 12% of patients had severe and 4% very severe clinical pictures (Cebalo et al., 2003). Also, a significantly higher percentage of asymptomatic infections in humans were caused by PUUV (69.8%) than by DOBV (17.5%) (Hukic et al., 2011).

The most common findings were fever, chills, malaise, myalgia, back and abdominal pain, headache, vomiting, diarrhea, blurred vision, oliguria followed by polyuria (Avšič-Županc et al., 1999; Markotić et al., 2002b). Blurred vision, acute renal failure, diarrhea and melena were significantly more often registered in patients with DOBV infection in Croatian patients (Markotić et al., 2002b). However, in Slovenian patients, blurred vision was significantly more often recorded in patients with PUUV infection (Avšič-Županc et al., 1999). Most Croatian PUUV infected patients had elevated systolic blood pressure on admission to the hospital while patients infected with DOBV had normal blood pressure. Patients with DOBV infection more often required hemodialysis, developed shock and death. Pathologic electrocardiography (ECG) was significantly more often found in patients with DOBV infections (Markotić et al., 2002b). Both, Croatian and Slovenian patients, infected with DOBV had a significantly lower number of platelets and higher levels of creatinine than PUUV-infected patients. All patients had elevated liver transaminases and Slovenian DOBV infected patients had significantly higher alanine aminotransferase (ALT) levels, while Croatian DOBV infected patients had significantly higher total bilirubin levels (Avšič-Županc et al., 1999; Markotić et al., 2002b).

Wide spectrum of clinical symptoms and signs, as well as clinical laboratory parameters observed among DOBV or PUUV causing HFRS might be at least in part related to different immune responses and viral load kinetics. Recent findings pointed toward notable differences between PUUV and DOBV infections, in terms

of viral load and antibody and cytokine response dynamics, all of which may be reflected in differing disease severities and clinical outcomes. Measuring viral RNA in patient samples revealed that viremia lasts for longer than previously believed, with DOBV or PUUV infected patients having viremia lasting on average 30 days or 16 days, respectively. DOBV infected patients were found to have a higher viral load than the PUUV infected patients. Both DOBV and PUUV infected patients had IgM at the time of hospital admission, but there was a difference in IgG antibody dynamics, with only a minority of DOBV infected patients having IgG antibodies. However, elevated levels of IL-10, TNF-α and IFN-γ were detected in peripheral circulation of all HFRS patients regardless of the causative agent. In DOBV infected patients the decrease in cytokine secretion level appeared around day 20 post-infection, while in PUUV infected patients the change was earlier (Korva et al., 2013b). In contrast, some of our unpublished results indicated that some cytokine soluble receptors could be increased in DOBV infected patients. Previous studies showed increased expression of both early and late T-cell activation antigens, e.g. CD25, CD71 and HLADR, memory cells and sCD23, which positively correlated with biochemical parameters (AST, ALT, urea, a2-globulin) during the acute phase of HFRS. The phenotypic changes observed, especially early and late T-cell activation markers, as well as memory cells, could be useful parameters in the evaluation of the HFRS course, and prognostic factors of HFRS severity. No significant differences were found between patients infected with PUUV or with DOBV (Markotić et al., 1999).

It is well known today that after HFRS in a certain percentage of patients chronic squeal could be observed. A 10-year follow-up study in B&H showed that renal function in HFRS patients was in normal limits, although after DOBV/infection, glomerular filtration rate was significantly lower than after PUUV infection (Tulumovic et al., 2010). However, our 16-year follow-up study revealed additional parameters of renal impairment in previous PUUV infected patients (A. Markotić, unpublished results).

4.2. HFRS a systemic disease

HFRS is a systemic infectious disease targeting different organs and organ systems. Analyzing clinical records of HFRS patients in the Balkans, we noticed that in a certain percentage of patients a symptoms and signs related to different organs and organ systems are found (Table 2). Some central nervous system symptoms, like headache, are usual for HFRS, but some other like epileptic seizures accompanied with pathologic electroencephalography (ECG) or intracerebral bleeding have been recorded as well (Avšič-Županc et al., 1999; Cerar et al., 2007; Markotić et al., 2002b; Pal et al., 2005). Endocrine disorders are not detected very often, but hypopituitarism with atrophic pituitary gland was reported as a late complication of HFRS (Pekic et al., 2005). Respiratory symptoms appear frequently and are especially connected to PUUV infection. Besides cough and sneezing in some patients, in about half of HFRS patients we can find pathologic pulmonary X-ray findings, such as pneumonitis presented with interstitial inflammatory infiltrates and sometimes pleural effusion (Avšič-Županc et al., 1999; Markotić et al., 2002b). Cardiovascular disorders are hallmarks of HFRS pathophysiology. Transient ECG changes are recorded in about 40% of HFRS patients, mostly in the oliguric phase (Markotić et al., 2002b; Pal et al., 2005; Puljiz et al., 2005). Although, we usually do not see five HFRS phases in our patients, hypertension could develop at the beginning of the diseases, followed by hypotension and shock in severe cases (Avšič-Županc et al., 1999; Markotić et al., 2002b). Some gastrointestinal symptoms appear in all HFRS patients and can cause difficulties in diagnosis at the beginning of HFRS. Strong abdominal pain, followed by gastrointestinal bleeding can direct diagnosis toward some surgical diseases. Liver disorders, like hepatomegaly and elevated liver transaminases and bilirubin have been frequently diagnosed in HFRS patients. However, there is a huge gap in our understanding of liver disorders in HFRS and its possible role in the pathophysiology of disease (Avšič-Županc et al., 1999; Markotić et al., 2002b; Papa et al., 2010). Acute pancreatitis was observed in DOBV infection as well (Puca et al., 2012). Another hallmark of HFRS in the Balkans, like in other parts of the world, is renal disorder. Elevated levels of urea and creatinine are helpful in early HFRS diagnosis. Oliguria is common in at least one third of patients and anuria and acute renal failure require temporary hemodyalisis (Avšič-Županc et al., 1999; Markotić et al., 2002b). Also, pathologic renal ultrasounds characterized with kidney enlargement, renal edema and hypotonia of the canal system are observed (Table 2) (Markotić et al., 2002b). Recently, we compared different initial clinical symptoms and laboratory findings in patients who developed oliguric acute renal failure (ARF) with those in patients who did not develop oliguric ARF. We identified the following risk factors for the development of oliguria and anuria on multivariable analysis: conjunctival hyperaemia or bleeding (relative risk (RR) 1.84, 95% CI 1.09–3.10; p 0.023), diarrhea (RR 1.45, 95% CI 1.07–1.97; p 0.017), serum sodium of Ł133 mM (RR 2.21, 95% CI 1.34–3.64; p 0.002), and dipstick protein values of >1.5 g/L (RR 1.59, 95% CI 1.09–2.33; p 0.016), as well as hiking in the forest (RR 1.92, 95% CI 1.13–3.26; p 0.016). Our findings may help physicians in the earlier identification of patients with a more severe form of HFRS caused by PUUV or DOBV (Turcinov et al., 2013).

Due to such diversity of clinical signs and symptoms the list of differential diagnosis is long: acute renal failure of another etiology, acute febrile urinary tract infection, tubulointerstitial

Table 2
HFRS as multisystemic disease in South-East Europe.

CNS/ocular disorders	Blurred vision Headache Pathologic electroencephalogram (epileptic seizure) Intracerebral bleeding
Endocrine disorders	Hypopituitarism
Respiratory disorders	Cough Sneezing Pathologic lung X-ray (interstitial inflammatory infiltrate, pleural effusion, discoid atelectasis)
Cardiovascular disorders	Pathologic electrocardiography (mild disorders of intraventricular conduction, non-specific alteration of the final complex, nonspecific depolarization disorders, sinus tachycardia in febrile stage, bradycardia-oliguric stage, intraatrial conduction disorders, apicarditis) Hypertension Hypotension Shock
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhea Melena Abdominal effusion Hepatomegaly Elevated liver transaminases and total bilirubine Acute pancreatitis
Renal disorders	Oliguria Anuria Renal failure Elevated urea and creatinine Pathologic renal ultrasonography (renal edemy, parenchymal stretching, kidney enlargement, diffuse lesion of the parenchyma, hypotonia of the canal system)

nephritis of other etiology, acute and chronic glomerulonephritis, acute abdomen, including appendicitis, hemorrhagic scarlatina, hemolytic uremic syndrome (HUS), thrombocytopenic thrombotic purpura (TTP), acute respiratory infections, sepsis, other hemorrhagic fevers (e.g. Congo–Crimean hemorrhagic fever in Bulgaria, Albania, Kosovo, Greece) (Christova et al., 2013; Markotić et al., 1996, 2002b; Sargianou and Papa, 2013). However, leptospirosis is in the first place in differential diagnosis of HFRS in the Balkans. Both causative agents have the same rodent reservoirs, both are endemic in South-East Europe and have almost the same symptoms and clinical laboratory findings at the onset of disease. Patients with leptospirosis usually have calf pain and higher levels of ALT, AST and especially total bilirubin (Markotić et al., 2002a; Sion et al., 2002). The phenotypic changes (increased early T-cell activation markers in HFRS patients), could be useful parameters to distinguish the two diseases in the early acute phase (Markotić et al., 2011). Dual infections should be considered as well with more severe clinical pictures (Markotić et al., 2002a).

In support to our hypothesis that immune status may be responsible for disease severity is an unusual outbreak recorded in 2002 among former intravenous drug users in a drug treatment community Susret, Ivanovac, northeast of Croatia. A man aged 30 years developed severe HFRS with fulminant systemic hemorrhage and acute renal failure, and died. Other HFRS patients developed mild or moderate disease. About 55% of community members were infected with either hepatitis B virus or hepatitis C virus, or both. Interestingly, 82% of the HFRS patients were infected with one or both types of hepatitis virus (Medved et al., 2002).

5. Treatment

Currently there is no specific therapy for HFRS. Symptomatic treatment with careful and balanced liquid and salts replacement is important. Acetylsalicylic acid and non-steroid anti-inflammatory drugs should be avoided. Instead, paracetamol should be used for fever or pain treatment when necessary. In case of a severe clinical picture, patients should be managed in a intensive care unit and temporary haemodialysis in cases of acute renal failure and anuria could be required (Markotić, 1996).

6. Prevention

Human behavior plays a critical role in the chance for hantavirus infections. Epidemiological investigations of risk factors for human infections revealed that professions related to forestry, farming, military activities or outdoor activities such as camping or using summer houses and hiking were identified as risk factors (Watson et al., 2014). Further risk factors include seeing rodents and their excreta, cleaning and working in barns and woodsheds, cleaning basements and gathering firewood. Thus, prevention of hantavirus infections is based on awareness and personal preventive measures to avoid virus-contaminated dust during work or leisure time, on proper cleaning and disinfecting areas containing rodent droppings and on continuous rodent control in and around human dwellings. In addition, minimizing food available to rodents around residential areas is known to effectively reduce the rodent population (Kraigher et al., 2012). Some of the Balkan countries had public health institutional guidelines on preventive measures available and they communicate preventive measures using a variety of media in case of an outbreak.

There is currently no hantavirus vaccine licensed in Europe. Research in molecular vaccine development is in process with candidate vaccines under phase I testing, but there are technical, regulatory and economic problems which need to be solved before a vaccine would become available (Schmaljohn, 2012). The Balkans represent an area with a potential need for hantavirus vaccines, but due to the co-existence of DOBV and PUUV causing HFRS in the same region, a two-component vaccine is required (Schmaljohn, 2009).

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